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Bariatric Surgery in the Era of Personalized Medicine

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Obesity represents a public health crisis. While the Food and Drug Administration approved two weight loss drugs in 2012, bariatric surgery will likely remain the most efficacious treatment for the morbidly obese. Bariatric surgery is prescribed for class III obesity [body mass index (BMI) ≥ 40 kg/m²] or class II obesity (BMI 35–39.9 kg/m²) associated with life-threatening co-morbid disease, such as type 2 diabetes, cardiovascular disease or cardiopulmonary problems. Roux-en-Y gastric bypass (RYGB), the most commonly utilized bariatric operation, divides the stomach into a small upper pouch and rearranges the small intestines producing dramatic weight loss primarily by reducing food intake¹. RYGB is being used with increasing frequency in the United States. The American Society for Metabolic and Bariatric Surgery estimated that 220,000 of these procedures were performed in 2005.

Despite its frequent use, questions remain about how RYGB regulates feeding behavior; in addition, some data suggests that RYGB produces insulin-sensitizing actions independent of weight loss¹. Another issue is variable outcomes following bariatric surgery. Most patients lose >50% of excess weight, a minority of patients achieve “ideal” body weight, while a smaller minority of patients achieve suboptimal results (<50% excess weight loss). Variability also applies to improvements, remission and relapse of co-morbid diseases, including type 2 diabetes^{2, 3}. Determining the mechanisms involved in mediating reduced appetite, improvements in insulin sensitivity, and variable responses to surgery therefore remain important objectives.

Zechner *et al.* combine basic research using genetically altered mice and human genetic epidemiology to investigate the role of melanocortin-4 receptors (MC4R) in mediating the effects of RYGB⁴. *MC4R* haplo insufficiency is the most common monogenic cause of human obesity⁵. Several SNPs located adjacent to the *MC4R* locus have been identified that are associated with altered BMI in humans⁶. Studies in mice suggest that MC4Rs regulate both sides of the energy balance equation, controlling food intake and energy expenditure^{5, 7, 8}. These studies also suggest that the central nervous melanocortin system regulates glucose and lipid metabolism independently of altered food intake or body weight. Consequently, several groups have investigated the role of MC4R in the effects of RYGB by examining the response of mice lacking functional MC4Rs (*Mc4r*^{-/-}) to experimental

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models of RYGB^{4,9} and the associations between MC4R polymorphisms with surgical outcomes. Collectively, these studies suggest that activation of MC4Rs play a role in surgically-induced weight loss effects, but do not preclude using this procedure for treating obesity due to *MC4R* haplo insufficiency.

Another study reported a rebound in body weight in *Mc4r*^{-/-} mice following RYGB which is not observed in “diet-induced obese” (DIO) control mice, while heterozygous (*Mc4r*^{+/-}) mice retain a normal response⁹. Zechner *et al.* reach a similar conclusion, however their approach differs in the genetic model employed and methodical analysis of metabolism. The *LoxTB Mc4r* mouse permits study of the involvement of MC4Rs specifically expressed by autonomic neurons. The assessment of metabolic outcomes was also more rigorous. Glucose homeostasis was assessed by measurements of endogenous glucose production, glycogenolysis and insulin signaling, while energy expenditure was also measured using indirect calorimetry.

The *LoxTB Mc4r* model has produced important information on the neuroanatomical substrates underlying melanocortin functions in the central nervous system (Figure 1). Expression of the bacteriophage Cre protein reactivates the *LoxTB Mc4r* allele. Restoring expression of the *LoxTB Mc4r* allele in the paraventricular nucleus of the hypothalamus using *Sim1-Cre* improves obesity by rescuing the hyperphagia observed in *Mc4r* null mice, but does not restore regulation of energy expenditure¹⁰. The *ChAT-Cre* transgene targets cholinergic preganglionic parasympathetic neurons of the dorsal motor nucleus of the vagus (DMV) and sympathetic preganglionic neurons in the intermediolateral nucleus of the thoracic spinal cord (IML). The DMV regulates vagal efferents serving the pancreas and digestive tract, amongst others. Projections from the IML are a component of the sympathetic nervous system. *Phox2B* is a homeo domain transcription factor expressed in the central nervous system; *Phox2B-Cre* reactivates the *LoxTB Mc4r* allele in preganglionic parasympathetic neurons of the DMV. Reactivation of the *LoxTB Mc4r* allele in the DMV using *Phox2B-Cre* results in modest improvements in hyperinsulinemia but not hyperglycemia associated with loss of MC4R function¹¹. In contrast, reactivation of the *LoxTB Mc4r* allele in the DMV and IML using *ChAT-Cre* results in pronounced improvements in hyper insulinemia and hyperglycemia and increases energy expenditure. In addition, reactivation of the *LoxTB Mc4r* allele in the DMV and IML using *ChAT-Cre* results in improvements in the control of hepatic glucose production by insulin. MC4Rs expressed by cholinergic sympathetic preganglionic neurons are thus important for controlling energy expenditure and preserving insulin sensitivity.

The current study replicates these outcomes, and also finds evidence that RYGB increases energy expenditure consistent with published data in rodent and humans¹²⁻¹⁴. Zechner *et al.* demonstrate that this effect occurs via activation of MC4Rs expressed by cholinergic sympathetic preganglionic neurons. In the current study, the authors did not use the *Sim1-Cre* transgene to investigate the role of MC4Rs in reducing appetite, probably because the effects of RYGB in their model appear to be primarily metabolic. In their hands, RYGB did not reduce food intake in obese mice. Rather, weight loss associated with RYGB appears to primarily result from increased energy expenditure. This response is attenuated in homozygous carriers of the *LoxTB Mc4r* allele, and was restored in mice where the *LoxTB Mc4r* allele was reactivated using the *ChAT-Cre* transgene. They also report the I215L variant in the human *MC4R* locus, associated with increased basal activity *in vitro*, correlates with greater weight loss and improvements in insulin sensitivity following RYGB. These results may represent an important step towards identifying genetic predictors of outcome after bariatric surgery. In addition, these findings add to the growing body of literature describing mechanisms underlying the relationship between surgically-induced weight loss and diabetes remission.

Genetic differences among patients undergoing bariatric surgery might provide an explanation for variable outcomes. This is not a new concept-genetic variability has been implicated in the predisposition to many clinical phenotypes and diseases, including obesity¹⁵. That genetic variation may also contribute to the variability observed in outcomes after RYGB is supported by published data^{16–19}. Determining whether genetics can be used to categorize the response of individuals to weight loss therapies, including gastric bypass surgery, could help optimize treatment choices for morbidly obese patients. Such studies might also yield new insights into mechanism.

Identification of predictors of diabetes remission after bariatric surgery is of particular importance because of the disproportionate impact of diabetes on public health. Genetic predictors of remission would allow for improved selection of patients most likely to benefit, given that surgery is a limited resource. Such predictors would also aid patient decision-making, as diabetes remission is often a dominant motive for surgery, which some patients might forgo if remission was unlikely.

Weight loss-independent improvements in insulin resistance after RYGB may involve altered secretion of gut incretin hormones that regulate glucose homeostasis (Figure 1). Bariatric operations that involve lesser alterations in gut anatomy, such as gastric banding, have fewer effects on incretin physiology and are associated with less improvement in insulin resistance¹. While incretins clearly play a role in diabetes remission after surgery, it is important to note that the magnitude of this effect in humans remains unclear; rigorous trials are lacking and data from human and animal models are conflicting¹. Moreover, the oft-cited observation that diabetes improves rapidly after gastric bypass is by no means universal. A substantial subset of gastric bypass patients experience slower improvement that correlates directly with weight loss, while a minority experience minimal improvement in diabetes despite substantial weight loss. Finally, gastric banding and sleeve gastrectomy, operations that are thought not to alter incretin physiology to the same degree as RYGB, none the less improve diabetes in most cases.

These observations demonstrate that like weight loss, variability exists in the response of diabetes to bariatric surgery and underlying mechanisms of diabetes remission are multiple. Zechner *et al.* demonstrate that this variability in outcome is determined in part by a specific SNP within the *MC4R* gene. They also demonstrate that anatomic selective restoration of MC4R function improves insulin sensitivity after gastric bypass, suggesting a potential mechanism disconnecting the regulation of glucose homeostasis and body weight. These observations lend credence to the concept that physiologic mechanisms exist that mediate diabetes resolution after surgery independent of weight loss. Future studies of incretin physiology in similar murine gastric bypass models, along with further study of the role of selective restoration of MC4R in the context of other bariatric operations not thought to affect incretin physiology, will clarify whether the effects observed by Zechner *et al.* involve incretins or represent a novel mechanism of weight loss-independent diabetes resolution.

Bariatric surgery has increased dramatically in the past two decades due to data demonstrating decreased long-term mortality and disease burden and cost-efficacy^{20, 21}. From a practical stand point, however, adequate resources in the form of health care dollars and surgeons simply do not exist to offer surgery to all candidates. Patient selection is therefore of critical importance. In addition, an understanding of the mechanisms underlying surgically-induced diabetes remission will lead to novel pharmacologic therapy for diabetes. The findings of Zechner *et al.* implicate MC4R as one such mechanism, and also identify an *MC4R* SNP as a predictor of diabetes remission. This represents a first step towards developing tools that will usher in the era of personalized medicine in the field of obesity and bariatric surgery.

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Figure 1.

Schematic showing the potential role of the central nervous melanocortin system in the anorectic and metabolic consequences associated with RYGB. The central nervous melanocortin system is comprised of neurons expressing pro opio melanocortin (POMC), agouti-related peptide (AgRP), or the melanocortin receptors (not shown). Studies using the *LoxTB Mc4r* mouse suggest that MC4Rs expressed in the paraventricular nucleus of the hypothalamus (PVN) are important for regulating satiety; the activity of MC4Rs expressed on preganglionic autonomic neurons controlling the parasympathetic and sympathetic nervous system (PNS, SNS) impacts on energy expenditure and insulin sensitivity in the periphery. RYGB is associated with altered secretion of gut peptides that changes the

activity of POMC and AgRP neurons to reduce food intake and improve insulin sensitivity by increasing autonomic tone^{7,8}.